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Chemoprophylaxis in malaria: drugs, evidence of efficacy and costs

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ABSTRACT

This review concentrates on different aspects of malaria chemoprophylaxis, namely drug combinations, resistance, impact of malaria prevention in pregnancy and cost effectiveness. A MEDLINE search was performed for all articles with the key word 'Malaria' in the title field and 'Prophylaxis' in any field. The search was restricted to articles published in English within the last decade (1999–2009). Data sources included review articles published in core clinical journals, cohort studies, interventional studies, case control studies and cross sectional analyses. The mechanism of action, trial evidence of efficacy, side effects and geographical distribution of resistance is discussed for each prophylactic drug regimen. Impact of prophylaxis in pregnancy and the cost considerations are discussed under two separate sub topics.

1. Introduction

Mortality and morbidity due to malaria is still substantial in many tropical countries. In 2006, 247 million cases of malaria were estimated, resulting in 881 000 deaths[1]. Of the 109 endemic countries, 30 countries in sub-Saharan Africa and five in Asia account for 98% of malaria deaths globally[2]. Yet, the actual burden of disease in these areas is not known due to under-reporting. It is estimated that the total incidence of malaria is decreasing in Bhutan, Sri Lanka, Thailand and North Korea, while the number of *Plasmodium falciparum (P. falciparum)* infections has risen in Bangladesh, India, Myanmar and Timor Leste[1]. Large-scale preventive campaigns, focusing on vector control, chemotherapy, and education have been used in the battle against this protozoan parasite which, with its innate complexities, continuously challenges human populations.

This paper concentrates on chemoprophylaxis and its consequences on the disease burden of malaria. In an ideal situation, such chemoprophylaxis should prevent all cases of malaria, be well tolerated and cost effective. If properly administered, it should prevent mortality and morbidity from malaria. However, such a perfect chemoprophylactic agent does not exist. This fact is made evident by the widely varied chemoprophylactic regimens recommended for different parts of the world. Different genetic mutations, and the selection pressure for these mutations, have rendered several drugs and drug combinations useless in some settings. As for side effects and toxicity, many drugs used in prophylaxis have disturbing side effects, including gastrointestinal, neurological and haematological disturbances[3]. These factors make it difficult to recommend a universally acceptable prophylactic regimen against malaria. Specific drugs or drug combinations for malaria prophylaxis have to be defined for each region, taking into consideration locally prevalent parasite mutants, cost effectiveness and public acceptance; this is a continuous challenge.

2. Methods

A MEDLINE search was performed for all articles with the key word 'Malaria' in the title field and 'Prophylaxis' in any field. The search was restricted to articles published in English within the last decade (1999–2009). There were 2 621 abstracts in the original search with these restrictions. The software Endnote X2 was used to filter articles. Bibliographies of cited literature were also

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searched. All abstracts were read independently by the three authors, and key articles were identified based on a consensus among all authors. Related or cited papers were also included. Sources were screened for relevance to the topic (articles based on chemoprophylaxis with reference to individual drugs or combinations, their use in pregnancy and evidence on cost effectiveness). Data sources included review articles published in core clinical journals, cohort studies, interventional studies, case control studies and cross sectional analyses. The epidemiological data were downloaded from the websites of international agencies, such as the World Health Organization (WHO).

3. Protection against clinical malaria

Various drugs and their combinations have been assessed in the prevention of clinical malaria. Currently, chloroquine, proguanil, mefloquine and doxycycline are all used for standard prophylaxis[4]. However, the success of these regimens depends on the drug-sensitivity patterns of local strains of *Plasmodium*. The following subsections discuss the specific issues related to each drug or combination used in the prophylaxis of malaria.

4. Chloroquine

Chloroquine has been used since the 1940s in the treatment and prophylaxis of malaria. This drug is concentrated within the food vacuole of the parasite (where haemoglobin is degraded) and inhibits the polymerization of toxic heme to hemazoin[5]. Chloroquine is indicated for treatment and prevention of all types of malaria where sensitivity persists [6]. Unfortunately, resistance to chloroquine is widespread, particularly for falciparum malaria. Resistance is mainly determined by the selection of a mutant form of the *P. falciparum* chloroquine resistance transporter gene (pfcrt) which effects chloroquine transport across the digestive vacuole of the parasite[7]. In many sub-Saharan countries, chloroquine is virtually ineffective as a prophylactic agent. A few countries in Central America and Central Asia still maintain complete sensitivity to chloroquine[6].

Chloroquine resistant vivax malaria is another problem. It was first reported from Papua New Guinea in 1989[8]. Since then cases have been reported from a vast geographical area spanning the continents of Asia (Indonesia, Myanmar, India and Turkey), Africa (Ethiopia) and South America (Brazil, Peru, Colombia). In all these areas, chloroquine resistant falciparum malaria is also reported and therefore chloroquine is not recommended for prophylaxis[6].

The side effect profile of chloroquine is well established and common problems include gastrointestinal disturbances and blurred vision. Though less common, other adverse effects include chloroquine-induced retinopathy, pruritus and mood changes[3].

Given the extent of resistance, despite being a safe and cheap choice, chloroquine alone cannot be recommended for prophylaxis in many endemic malaria regions today.

5. Mefloquine

Mefloquine was introduced in the 1970s as a synthetic analogue of quinine. Its exact mechanism of action is unclear. However, it is thought to form toxic complexes with heme, which damage the membranes of the parasitic organelles[9]. Mefloquine is used mainly in the treatment and prophylaxis of chloroquine resistant malaria, and trials have shown it to have good efficacy in this regard[10]. However, *P. falciparum* resistance to mefloquine has also been reported (though not widespread), making it less useful as a prophylactic agent in some areas of South East Asia [11]. Again, the exact mechanism of resistance is unclear, but mutations in the *P. falciparum* multiple drug resistance gene (pfmdr1) are implicated[12-16].

Another deterrent to its use are its side effects, in particular neuropsychiatric effects. It is known to cause severe depression, anxiety, insomnia, nightmares, seizures and neuropathy. However, several studies comparing the side effect profile of mefloquine with other standard regimens have concluded that, in doses used for prophylaxis, it is no more toxic than other therapies[17]. Indeed, it was found to be more tolerable than doxycycline when considering both neuropsychiatric and gastrointestinal side effects[18].

Mefloquine can be recommended for prophylaxis in many malaria areas of the world. Despite some disturbing side effects, the risk-benefit assessment supports its use in malaria prevention.

6. Sulfadoxine-pyrimethamine (SP)

The combination of sulfadoxine and pyrimethamine has been used in the treatment and prevention of malaria since the 1970's. These antifolate drugs have a long half-life and their presumed mechanism of action involves interfering with folate metabolism of the parasite by inhibiting the dihydrofolate reductase (DHFR) and dihydropteroate synthatase enzymes[19]. Its indications include prophylaxis and treatment of drug-resistant chloroquine malaria. However, SP is a failed drug for prophylaxis in many sub Saharan regions[20,21]. The mechanism of resistance is attributed to mutations in the parasite genes encoding the enzymes of folate metabolism. Nonetheless, SP has a special indication in prophylaxis. In areas with stable *P. falciparum* malaria in Africa, WHO recommends a regimen known as intermittent preventive therapy (IPT) for pregnant women, infants and children (see subsection on pregnancy). SP is the only recommended drug for such therapy in Africa based on trial evidence[19,22]. The exact mechanism of action of SP in IPT is unclear, but is thought to be related to its ability to clear the parasite and suppress asymptomatic infections. The longer half life due to slow clearance enables it to maintain an efficacious plasma concentration over a longer period of time compared with other drugs/combinations. This may prevent the occurrence of new infections in the weeks following its administration.

However, the emerging patterns of resistance and the side effect profile have caused concern with regards to the

continued use of SP. The potentially serious side effects of SP include haematological problems, such as megaloblastic anaemia, thrombocytopaenia and leucopaenia, pulmonary infiltrates with eosinophilia, peripheral neuropathy, and cutaneous manifestations, such as Stevens-Johnson syndrome[3].

Current opinion on the use of SP in prophylaxis is that it should be restricted to the special indication of IPT. It is not recommended for travelers to endemic areas[3, 6].

7. Proguanil and its combinations

Proguanil was developed in the late 1940s and its mechanism of action involves inhibiting the dihydrofolate reductase enzyme of the parasite and blocking DNA synthesis. However, when given alone, resistance can develop rapidly against it[4]. Therefore, it is used in combination with either chloroquine or atovaquone (which has a different mechanism of action against the parasite) to treat and prevent chloroquine resistant malaria.

In combination with chloroquine, proguanil has been shown to reduce the clinical burden of malaria significantly compared to a placebo[23], but has also been shown to be less efficient than mefloquine or atovaquone-proguanil combination[10]. Resistance to this combination has been a problem due to the pfcrt mutation affecting the chloroquine component, and, hence, currently, it is not the preferred choice of prophylaxis in sub Saharan Africa[6]. The main side effects include gastrointestinal disturbances (including nausea, diarrhoea and stomatitis) and rarely cholestasis.

On the contrary, the combination of atovaquone-proguanil (malarone) was shown to have excellent efficacy in prophylaxis, particularly against falciparum malaria, with a good safety profile in several trials[24, 25]. Nonetheless, evidence for prophylactic failure with malarone emerged in the 2001-2005 period. Though this observation is not evidence of widespread resistance to malarone, it can be a potential problem in the future as there could be many locals infected with these resistant strains. It has been demonstrated that mutations in the cytochrome b gene (which codes for the mitochondrial enzyme involved in cellular respiration and is critical for survival) is associated with delayed recrudescence of the parasite with malarone [26].

The main side effects of malarone include gastrointestinal disturbances, insomnia, dizziness and headache. Overbosch *et al*[27], in a large-scale, randomized clinical trial, have shown that the protective efficacy of this combination was as good as that of mefloquine, with comparatively less side effects, in particular with regard to gastrointestinal disturbances and stomatitis. Riemsdijk *et al*[28] have also shown that a mefloquine treated group had higher scores of depression, anxiety and anger compared with those on malarone treatment.

8. Primaquine

Primaquine has a somewhat different role in the chemoprophylaxis of malaria. The drug has been used since the 1950s, although its mechanism of action is not yet fully understood. Theoretically, the indications for primaquine, as supported by trial evidence, are three-fold. It can be used as a primary prophylactic agent, as a terminal prophylactic agent and in radical cure regimens for ovale and vivax malaria . Resistance to primaquine is rarely reported[29].

However, there are two factors limiting its use as a primary prophylactic agent; side effects and cost. The major side effect of primaquine is its ability to precipitate glucose 6 -phosphate dehydrogenase (G6PD) deficiency. It is not cost effective for prophylaxis when costs of testing for G6PD status of recipients are considered[30]. Furthermore, its use in pregnancy is contraindicated as the G6PD status of the foetus cannot be routinely assessed[31]. Thus, primaquine is currently not recommended by the WHO for primary prophylaxis[6].

Nonetheless, primaquine has a place in chemoprophylaxis in several special situations. Firstly, in patients with *Plasmodium vivax (P. vivax)* or *Plasmodium ovale (P. ovale)* infection treated with anti-malarials, despite the clearance of blood parasites, relapses could occur due to the reactivation of hypnozoites in the liver (*P. falciparum* does not have hypnozoites in its life cycle). Primaquine is used to eliminate the hypnozoites of *P. vivax* and *P. ovale* species, thus preventing clinical relapses. Since vivax malaria is the more prevalent form of malaria outside of Africa, particularly in Asia, primaquine plays a role in preventing clinical disease in such areas.

Secondly, primaquine has been suggested to have a role in terminal prophylaxis (medication taken towards the end of the exposure period). Chloroquine and primaquine are usually used in combination for this purpose on the premise that chloroquine enhances the hypnozoite clearance effect of primaquine. However, Soto *et al*(1999). have demonstrated that the combination of primaquine and chloroquine did not add to the protective efficacy against falciparum malaria, or, more surprisingly, against vivax malaria (as *P. vivax* was sensitive to chloroquine in this locality) when compared with primaquine alone. Though the trial was carried out in a limited number of individuals (<200), this interesting aspect has not been examined in detail by anyone else[32,33]. In our opinion, the role of primaquine in terminal prophylaxis (in adult, non-immune, non-pregnant travelers) needs to be re-assessed with regard to cost and benefit. Even if the costs of testing for G6PD status are considered, it might prove beneficial as local outbreaks from relapses in non-immune communities (after travelers return home) can be avoided.

Finally, primaquine can be used to prevent the transmission of falciparum malaria. In patients treated with chloroquine or artesunate, primaquine is effective in eradicating circulating gametocytes, which are infective to the vector/s. Thus, it acts as a chemoprophylactic agent at a community level by interrupting the transmission of falciparum malaria.

9. Antibiotics

Doxycycline is a semisynthetic tetracycline used in malaria prophylaxis. Its antibacterial action involves inhibition

of protein synthesis, and the same mechanism may kill plasmodia. Doxycycline is shown to have good efficacy in areas of chloroquine resistant malaria[34]. However, data on resistance patterns have not been reported.

There is concern about its side effects limiting compliance. The commonly reported side effects include gastrointestinal disturbances, flushing and tinnitus. It cannot be used in pregnant women, and its use in children is not advised due to dental staining. The preparation of doxycycline will also determine the severity of side effects. For example, doxycycline monohydrate caused less gastrointestinal disturbances than doxycycline hyclate and also had a better side effect profile than chloroquine- proguanil[34]. However, another trial by Sonmez *et al* has shown doxycycline to cause more side effects than mefloquine; the preparation of doxycycline was not mentioned in this paper[18].

Azithromycin is a macrolide antibiotic with limited evidence in malarial prophylaxis in comparison with doxycycline. It also acts by interfering with protein synthesis. Daily administration of azithromycin as a prophylactic regimen was shown to be effective against vivax malaria[35,36]. However, the evidence for protection against falciparum malaria is less convincing, as one trial had too few falciparum infections (four in azithromycin group and five in control group) to permit a valid statistical analysis[35]. Another trial showed a protective efficacy of only 71.6% against falciparum malaria (as opposed to a protective efficacy of 98.9% against *P. vivax*)[37]. Data on resistance patterns for azithromycin is not available. Its main side effects are gastrointestinal disturbances.

In summary, none of these drugs offer complete protection against malaria (depending on the geographical area). Chloroquine and SP resistance is widespread in many malarial areas. The combination of proguanil and chloroquine is recommended for some of these areas, but resistance is developing rapidly[6]. On the other hand, doxycycline, atovaquone-proguanil (malarone) and mefloquine are effective in many areas of multidrug resistant malaria. Compliance is another issue that has a direct impact on efficacy of various regimes. A less disturbing side effect profile, shorter duration of prescription and lesser frequency of therapy (daily vs weekly administration) would improve compliance.

10. Prophylaxis and pregnancy

It is estimated that 50 million women become pregnant annually in areas endemic for malaria, and 50% of them are in sub Saharan Africa[19]. Malaria in pregnancy carries many risks for the mother as well as for the baby, and such risks are greater in the first and second pregnancies[38]. Not only are these women vulnerable to severe malaria infection, but, once infected, the disease is more likely to progress to complications, including cerebral malaria and pulmonary oedema. Infection during pregnancy causes high parasitaemia, a greater degree of anaemia and a higher risk of stillbirth due to parasitic sequestration in the placenta. Therefore, the prevention of malaria during pregnancy, particularly in primigravidae, should be a priority in high prevalence regions. In general, travel to endemic regions is discouraged during pregnancy. However, in unavoidable circumstances, the benefits of prophylaxis have to be balanced against the risks of infection and the side effects of drugs.

Apart from tetracycline and related drugs, other drugs used in prophylaxis have not caused significant teratogenicity, and some authors consider them safe for use during pregnancy[31]. However, the wider consensus is that, where firm evidence for safety is lacking, especially for mefloquine and malarone, it is prudent to use an alternative unless the resistance patterns deems their use as essential[3, 6].

The possible combinations that may be used in pregnancy include chloroquine alone, chloroquine-proguanil, mefloquine, atovaquone-proguanil and SP[31]. However, in our opinion, data are still lacking to recommend atovaquone-proguanil (to be avoided unless essential) and mefloquine for widespread use in pregnancy. Primaquine is not considered safe for reasons mentioned previously.

The most efficacious combination of drugs depends on the locally prevalent *Plasmodium* species and resistance patterns and therefore varies between regions[39]. Chloroquine has been used over many years for prophylaxis against both *P. vivax* and *P. falciparum* infections during pregnancy with a well established safety profile. Despite widespread resistance, its use still has a positive impact on pregnancy outcomes (reduction in low birth weight, less maternal anaemia, reduced maternal parasitaemia) compared with no prophylaxis, presumably in people infected with sensitive strains[40,41]. A randomized placebo controlled trial for primigravid mothers in Uganda showed that weekly prophylaxis with chloroquine results in better outcome than passive case management in terms of improved maternal haemoglobin levels and improved birth weights of babies[42]. Salihu *et al*[40]. reported similar findings for chloroquine prophylaxis from a study in Cameroon. In this group, maternal parasitaemia declined significantly (26.3% *vs*. 44.9%) in the treatment group, and the low birth rates also declined, though not significantly (P=0.16). Studies of the use of chloroquine during pregnancy in Asia are few. Villegas *et al* conducted a double blind randomized trial (n=1 000) of weekly prophylaxis with chloroquine (300 mg base) *vs*. placebo for pregnant women (primigravid or multigravid) In Thailand[43]. The results have demonstrated that prophylaxis with chloroquine offers protection against vivax malaria. However, no significant difference was observed with relation to the occurrence of falciparum malaria compared with a placebo.

The combination of chloroquine with proguanil has been assessed in areas with chloroquine resistance, with good results. The disadvantage is that the chloroquine-proguanil combination needs to be administered over many weeks to maintain the protective effect, which could lead to resistance due to over-exposure. The evidence on safety of the atovaquone-proguanil combination is not well established to recommend its use during pregnancy.

Mefloquine has a teratogenic effect at high doses in animals. However, two studies in humans have not demonstrated any adverse effects. One trial in Thailand (trimester not specified) showed that the mefloquine group

was no different from a quinine-treated group in terms of adverse pregnancy events (*eg* preterm labour and foetal distress), and another small study on 20 women exposed to mefloquine in pregnancy in the third trimester showed no adverse outcome for infants after a follow up of 2 years[44, 45]. Both studies demonstrated no teratogenicity. However, the lack of exposure data in the first trimester calls for caution in its use[6].

As early as in 1994, it was shown that SP (Sulfadoxine 500mg and pyrimethamine 25 mg) administered in two intermittent doses during the second trimester and at the beginning of the third trimester was more effective in reducing peripheral and placental parasitaemia than the traditional long term prophylactic regimen of chloroquine[46]. The prolonged effect of the combination was partly attributed to the long half-lives of both components of the drug, though its exact mechanism of protection is not fully understood. Since the mid 1990s, this combination was adopted as the main mode of prophylaxis during pregnancy in many endemic areas of Africa and became known as intermittent preventive therapy (IPT). Though it has had a positive impact on preventing malaria to date, reports of emerging resistance have cast doubt on its future role in prophylaxis[47]. Another potentially unexplored, yet theoretically important issue, is the widespread use of cotrimoxazole in the treatment of HIV, which is shown to induce cross-resistance between sulfadoxine and sulfamethoxazole moieties and pyrimethamine and trimethoprim moieties[48]. The effects of the loss of efficacy of SP, which is the only recommended combination for IPT, would be considerable; a search for a replacement combination is urgently needed.

One alternative is the combination of chloroquine with azithromycin which has been shown to have synergistic activity (*in vivo*) against *P. falciparum* in trials in Africa and India (azithromycin 1 000 mg and chloroquine 600 mg daily for 3 days) when used in non pregnant adults[49, 50]. If used in IPT, both drugs are safe to be administered at any time during pregnancy with the additional benefits of preventing/treating sexually transmitted infections (STIs) and pneumococcal infections during pregnancy. There are two limiting factors in using this regimen for prophylaxis; the high cost of azithromycin and the risk of wide spread resistance to azithromycin with large scale population exposure. Also for parasitological clearance, the combination has to be taken over three days (unlike the single dose of SP) and ensuring compliance with direct observation may be problematic[51]. Clinical trials are yet to assess the practicality and efficacy of using this combination for IPT.

In summary, chloroquine and chloroquine-proguanil combination have been evaluated in numerous clinical trials and found to be efficacious in improving maternal and neonatal outcome and exhibiting a good safety profile. Sulfadoxine-pyrimethamine is used in intermittent prophylactic therapy in areas of stable *P. falciparum* transmission with efficacy, but resistance is becoming a significant problem. Currently, there is inadequate evidence of the safety and efficacy of mefloquine or proguanil-atovaquone for use during pregnancy. The use of either tetracycline group of antibiotics or primaquine is contraindicated during pregnancy.

11. The cost factor

The costs involved in malaria prophylaxis are not restricted to the monetary value (direct cost) of the drugs used. It also involves indirect costs such as laboratory tests (*eg* testing for G6PD deficiency before primaquine administration), costs of treatment in failure of prophylaxis, and costs of treatment of side effects. Our calculations for direct costs of short term prophylaxis of people traveling into endemic areas have shown that, without any terminal prophylaxis with primaquine, doxycycline is the cheapest regimen of those considered by the British Medical Association for travelers to endemic areas[3]. Chloroquine alone is very cheap but ineffective in many endemic areas. Mefloquine was twice more expensive than chloroquine-proguanil for a one week stay. Atovaquone-proguanil was the most expensive of all.

Queries have been raised about the cost effectiveness of non-selective prescription of prophylaxis to travelers going in to areas of low incidence (*eg* Sri Lanka). A survey in eight European countries has shown that the total number of infections imported from the Indian subcontinent (including India, Bangladesh, Pakistan and Sri Lanka) is less than 5% of the total number of malaria cases reported, and is on the decline[52]. Given the low risk, some authors argue that stopping non-selective prescription for travelers in to the subcontinent is more cost effective[52]. Though it can be argued that the low rate of infection is due to effective prophylaxis, another survey in departure lounges at European airports has shown that only 22% of travelers comply with prescribed/recommended prophylaxis regimens [53].

The situation is different for people living in areas endemic for malaria. While the choice of drugs is determined by the local resistance patterns, the duration of prophylaxis has to be long term and possibly annually with each transmission season. Benefits such as improvement of working capacity, reduction of low birth weight deliveries, cognitive development of younger generations and overall improvement of well-being become the major advantages in this setting. Some of these benefits are difficult to quantify in terms of money but nevertheless important. At the same time, considering the risks of long term prophylaxis is also pertinent. Retinopathy (with macular and perimacular degeneration) is known to occur with the long-term use of chloroquine, and prophylactic regimens have precipitated such morbidity. Polyneuropathy is another complication of long-term chloroquine use. Any serious side effect, even if not associated with long-term use, may cause concerns if a drug is to be recommended for widespread use (chloroquine: haematological abnormalities, dyskinesias, seizures, and hypotension; SP: Steven Johnson syndrome and blood dyscrasias). These complications make it difficult to analyze and formulate a cost-effective regimen applicable to a vast geographical area of high endemicity.

12. Conclusions

Mortality and morbidity from malaria show a significant shift from the situation three decades ago. The malaria burden in some regions, such as South Asia, has declined significantly while it is still a major cause of mortality and financial distress in sub Saharan Africa. Prophylaxis has implications in both these settings, to break the cycle of infection and move towards elimination in South Asia, and to reduce the disease burden in sub Saharan Africa. Unfortunately, resistant forms of the parasite have emerged against all regimens of prophylaxis used to date, and the problem is significantly greater in the most affected regions of Africa. The development of resistance against cheaper drugs of prophylaxis, such as chloroquine and SP, is widespread in several malaria hotspots.

Malaria prophylaxis has shown clear benefits in reducing maternal anaemia and the incidence of low birth weight in endemic countries. The cost effectiveness of universal prophylaxis for travelers into the subcontinent is controversial, given the low risk of infection; more selective prescription of prophylaxis will be useful. The cost effectiveness of prophylactic regimens for people living in endemic areas is difficult to estimate, because of the complex hidden costs and benefits involved. The importance of having a centralized government-controlled anti-malaria programme to limit the exposure of the human population to different drug regimens is demonstrated in two ways; to save money and to delay the emergence of resistance which ultimately results in a successful phase out towards elimination.

Two reliable sources for detailed information on malaria prophylaxis for travelers are the 'International Travel and Health Report, 2009' and the 'Travelers Health - Yellow book' which are published by the WHO and the Center for Disease Control (CDC) respectively[6, 54].

Areas needing further research are; assessing the efficacy and safety of prophylactic regimens in the elderly and the immunocompromised, quantification of the prevalence of resistance to individual regimens in endemic areas and options for replacing SP in intermittent preventive therapy.

Conflict of interest statement

We declare that we have no conflict of interest.

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